DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 18 are indefinite because they depend on canceled claims. For the purpose of this action, it is assumed that these claims depend on claim 43 but correction is required.

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 3, 5-16 and 18-21, 29, 35, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoppini et al. (US 5,958,762) in view of Minchinton (US 5,602,028).

Regarding limitations recited in claim 43 which are directed to the flow or a 'common well' of nutrient medium, it is noted that neither the manner of operating a disclosed device nor material or article worked upon further limit an apparatus claim. Said limitations do not differentiate apparatus claims from prior art. See MPEP § 2114 and 2115. Further, it has been held that process limitations do not have patentable

weight in an apparatus claim. See Ex parte Thibault, 164 USPQ 666, 667 (Bd. App. 1969) that states "Expressions relating the apparatus to contents thereof and to an intended operation are of no significance in determining patentability of the apparatus claim."

Regarding claims 3, 5, 6 and 43, Stoppini discloses an exposure device comprising a base portion (1) connected with a top portion (3) to form therebetween a medium chamber adjacent said base portion, a fluid exposure chamber adjacent said top portion which is contiguous and coextensive with said medium chamber, and a plurality of cell culture chambers (6) positioned between said medium chamber and said culture chamber (see fig. 1: the medium chamber is viewed to be the space below membrane 5, and the fluid exposure chamber is the space above membrane 5 and are viewed to be contiguous and coextensive with each other), said medium chamber being common to all culture chambers. The device further comprises a fluid inlet and outlet (sealing devices 4 and 4' are viewed as fully capable of acting as an inlet or outlet, as fluid flow could be initiated via a syringe or similar device) and a medium inlet and outlet (sterile septa 9' and 9" are viewed as medium inlets/outlets).

However, the reference does not explicitly disclose the device wherein the medium directing means is formed from a raised area of said base portion of said exposing device or is an island.

Minchinton discloses a similar device to Stoppini which comprises three cell culture chambers comprising a semi-permeable membrane. Minchinton also discloses that the chamber includes stirring means at the base of the chamber to vigorously stir

the liquid medium and move said medium to flow over both major surfaces of the membrane at a speed to adequately deliver nutrients to the cell culture adhered to and growing on one major surface of the membrane (see C2/L38-50 and fig. 1). The stirring means is disclosed as a magnetic stir bar (34).

As a magnetic stir bar would be capable of achieving fluid flow faster than some commercially available peristaltic pumps, it would have been obvious to one of ordinary skill in the art at the time of invention to incorporate into the device of Stoppini, a magnetic stir bar in order to generate sufficient fluid flow speeds to adequately fulfill the nutrient needs of particular cell cultures, as taught by Minchinton.

The magnetic stir bar of modified Stoppini is viewed as an island and a raised area of said base portion of the device and as an island within the medium chamber. It is further viewed as centrally located within the medium chamber and located equidistant to each of said culture chambers.

For claim 7, the device comprises three culture chambers.

For claim 8, the base of said culture chambers are spaced apart from the base of said device by a gap, which would allow nutrient medium to flow freely under the chambers.

For claim 11, the medium inlet is located in said base portion of said device.

For claim 12, the medium inlet is located in a sidewall of said base portion.

For claims 14-16 and 18, the medium inlet is viewed as a tube, the medium outlet is spaced apart from the inlet by all of said culture chambers and the medium outlet is viewed as fully capable of removing nutrient medium from a top surface.

For claim 21, the medium outlet is viewed as a tube.

For claim 29, the fluid exposure chamber is in flow communication with all said culture chambers.

For claim 35, the device further comprises a cell culture chamber support (membrane surface 8 is viewed as a support).

Regarding claims 9-10, modified Stoppini discloses all of the claim limitations as set forth above, but the reference does not explicitly disclose the length of the gap between the culture chambers and base portion. As the amount of nutrient medium and thus total nutrients available to the culture chambers are variables that can be modified, among others, by adjusting said gap length, amount of nutrient medium and thus total nutrients available to the culture chambers as the gap length is increased, the precise gap length would have been considered a result effective variable by one having ordinary skill in the art at the time the invention was made. As such, without showing unexpected results, the claimed gap length cannot be considered critical. Accordingly, one of ordinary skill in the art at the time the invention was made would have optimized, by routine experimentation, the thickness of the gap length in the apparatus of modified Stoppini to obtain the nutrient medium (and thus total nutrient capacity) of the device (In re Boesch, 617 F.2d. 272, 205 USPQ 215 (CCPA 1980)), since it has been held that where the general conditions of the claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. (In re Aller, 105 USPQ 223).

Regarding claim 13, modified Stoppini discloses all of the claim limitations as set forth above, but the reference does not explicitly disclose the medium inlet located in a bottom wall of the base portion. The reference only discloses the inlet in a side wall of the base portion. However, the placement of the medium inlet is strictly an engineering design choice that would have been obvious to one of ordinary skill in the art barring any unexpected results based on the exact placement of the inlet. **Specifically, a change in the placement of the inlets would create two identically functioning and thus equivalent embodiments.** Therefore, it would have been obvious to one of ordinary skill in the art at the time of invention to place the medium inlet in the bottom wall of the base portion of the device.

Regarding claims 19-20, modified Stoppini discloses all of the claim limitations as set forth above, but the reference does not explicitly disclose the medium outlet comprises two outlets. However, it would have been obvious to one of ordinary skill in the art at the time of invention to add an additional medium outlet in a separate location of the device in order to allow for quicker and more efficient medium removal. Additionally, regardless of the placement of the second (or more) outlet(s), they would necessarily be positioned to allow for both basal and submersion feeding of cell cultures within the cell culture chambers.

3. Claims 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoppini et al. (US 5,958,762) in view of Minchinton (US 5,602,028) as applied to claims 3, 5, 7-16 and 18-21, 29, 35, and 43 above, and further in view of Aufderheide et al. (A

method for in vitro analysis of the biological activity of complex mixtures such as sidestream cigarette smoke) and Rose et al. (US 4,792,378).

Regarding claims 30-34, modified Stoppini discloses all of the claim limitations as set forth above. The reference does not explicitly disclose an additional fluid dispersing means. Aufderheide discloses that studies of the cytotoxicity of air contaminants such as gaseous particles have traditionally used animal experiments because of the difficulties in exposing cell cultures directly to these substances (see abstract). Aufderheide further discloses that the Cultex system allows for the direct exposure of cigarette smoke to human bronchial epithelial cells to allow does-dependent effects to be measured (see abstract).

Rose discloses a gas dispersion disk (20) that includes an arrangement of apertures which are tailored to the particular pressure gradients existing within a reactor chamber to thereby provide a uniform flow of gas vapors to the various objects below it (see C4/L52-63).

It would have been obvious to one of ordinary skill in the art at the time of invention to provide a gas (fluid) dispersing means in a portion of the device of modified Stoppini, in order to provide a means for in vitro toxicology testing. This would allow for the dose-dependent measurement of cigarette smoke effects to human bronchial cell in vitro, as taught by Aufderheide. It would have further been obvious to one of ordinary skill in the art at the time of invention to use the fluid dispersion disk of rose in the apparatus of modified Stoppini, in order to create a uniform distribution of gas (fluid)

flow over the cell cultures. The use of a dispersion disk would necessitate that it be located above the cells to allow for uniform flow distribution.

Aufderheide further teaches that the fluid inlet is connected to a fluid generating means (see figure 7: smoking machine).

4. Claims 25-27 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoppini et al. (US 5,958,762) in view of Minchinton (US 5,602,028) as applied to claims 3, 5, 7-12, 14-16 and 18-21, 29, 35, and 43 above, and further in view of Gruenberg (US 5,627,070).

Regarding claims 25-27, modified Stoppini discloses all of the claim limitations as set forth above. Additionally, the reference discloses that perfusion of the nutritive medium takes place by means of an external peristaltic pump (see C2/L40-44). However, the reference does not explicitly disclose that there are two separate pumps attached to the medium inlet and outlet respectively.

Similar to Stoppini, figure 1 of Gruenberg teaches a cell growing device for in vitro cell population growth (see abstract). The device contains a recirculation mechanism (6), which contain stainless steel connectors (6a) which connect the inflow and outflow openings of cartridges (4, which are where the cells are maintained), see C10/L24-43). A centrifugal pump (44a) carries media through the stainless steel pathway to a regeneration mechanism (46) wherein media is replenished with nutrients and essential gases, and wherein waste products from cell growth are removed. A second pump (44b) directs the regenerated media to the cartridge inflow openings.

It would have been obvious to one of ordinary skill in the art at the time of invention to substitute the peristaltic pump of Stoppini, with the dual-pump recirculation/media regeneration system in order to allow the circulating media to be replenished, as taught by Gruenberg.

The two centrifugal pumps would be fully capable of operating at separate pump rates. Regarding the limitations of claim 27 which are directed to a manner of operating disclosed pump, it is noted that neither the manner of operating a disclosed device nor material or article worked upon further limit an apparatus claim. Said limitations do not differentiate apparatus claims from prior art. See MPEP § 2114 and 2115. Further, it has been held that process limitations do not have patentable weight in an apparatus claim. See Ex parte Thibault, 164 USPQ 666, 667 (Bd. App. 1969) that states "Expressions relating the apparatus to contents thereof and to an intended operation are of no significance in determining patentability of the apparatus claim."

Regarding claim 36, Gruenberg teaches that the recirculation tubing is made from stainless steel, as disclosed above. Therefore, part of the exposure device is made from stainless steel.

Response to Arguments

5. Applicant's arguments filed 12/30/09 have been fully considered but they are not persuasive. Applicant's remarks on page 8 are directed to a drawing objection and 112 2nd paragraph rejection. These are viewed as remedied and the respective objection and rejection are withdrawn. Applicant asserts on pages 9-10 that there is no outlet disclosed and that because device 4 and 4' are disclosed as 'sealing devices' that they

cannot function as an outlet. This is not convincing, particularly in light of the fact that the instant claims only require an 'outlet' which reads on a conduit (or sealing device as disclosed by the reference). Further, applicant's arguments to the reference teaching away from the claimed invention are not convincing because the instant claims and the cited structure are not structurally distinct as described above. Applicant's argument that Stoppini does not disclose medium directing means is moot in view of the combination of Stoppini and Minchinton as disclosed above. Applicant provides no specific arguments on pages 10-11 as to why the rejections of claims 9-10, 13, and 19-20 are improper other than those addressed above. Applicant's arguments regarding the addition of Minchinton are not convincing because a stirrer would provide additional fluid speeds which would increase nutrient transfer or additional speed which may not necessarily be obtained by the flow means. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In response to applicant's assertion that Aufderheide does not disclose a fluid dispersing means as disclosed in the application, it is noted that the reference discloses sufficient structure to meet the limitations set forth in the instant claims. Applicant makes the same arguments as to the structure relied upon in the

Rose reference which is equally non-convincing. In response to applicant's argument that Rose is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the problem applicant was concerned with was dispersion of a fluid which is also the purpose of the Rose reference. Additionally, applicant's assertion that different pump rates is not a process application is not convincing. The Gruenberg does not need to have a motivation that the pumps are fully capable of operating at different speeds and applicant has provided no evidence as to why the pumps would be incapable of operating at different speeds.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMESON Q. MA whose telephone number is (571)270-7063. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on (571)272-1374. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JM
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/Michael A Marcheschi/
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